IJPSR (2016), Vol. 7, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 May, 2016; received in revised form, 13 July, 2016; accepted, 27 July, 2016; published 01 October, 2016

FORMULATION AND *IN VITRO* EVALUATION OF SOLID DISPERSION OF FLUCONAZOLE

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Keywords:

Fluconazole, Solid dispersion, Mannitol, Carbopol 934, *In-vitro* drug release.

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ABSTRACT: The Goal of the present investigation was to design and evaluate gels for topical delivery of water insoluble antifungal agent Fluconazole with an aim to increase its penetration through skin and there by its flux. This is a broad spectrum imidazole derivative useful in the treatment of superficial and systemic fungal infections. The solubility of Fluconazole is increased by preparing solid dispersions with using mannitol, urea, polyethylene glycol 6000, polyvinyl pyrrolidone K30 and ß-cyclodextrin as carrier. Solid dispersion of Fluconazole was prepared by physical mixture method, solvent evaporation method, fusion method, Kneading Method and complex formation, *in-vitro* release profiles of all solid dispersions were comparatively evaluated and also studied against pure drug of Fluconazole. Faster dissolution was exhibited by solid dispersion containing 1:3 ratio of drug: mannitol by fusion method. The prepared solid dispersions were subjected for percent practical yield, drug content, infra red (I.R.) spectroscopic studies and differential scanning calorimetry (DSC). FT-IR spectra revealed no chemical incompatibility between drug and mannitol. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC). The formulation (FCS2) containing carbopol 934 (1%) with sodium lauryl sulphate 0.5% (500mg) showed best *in vitro* release of 98.95% at the end of 6 hrs.

INTRODUCTION: Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability [1].

Poorly water-soluble drugs present many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.7(10).4170-79

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.7 (10).4170-79

Solid dispersions have been widely reported as an effective method for enhancing the dissolution rate and bioavailability of poorly water soluble drugs [2]. Nearly one-third of drugs in development are water insoluble and one-half fail in trials because of underprivileged pharmacokinetics [3]. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and G.I. mucosal toxicity of drugs [4]. Poorly water soluble drugs belong to BCS class II and Class IV group of compounds [5].

In the process of absorption of drug from oral route dissolution is the rate limiting step for lipophilic drugs. Therefore it is necessary to enhance dissolution of these drugs to ensure maximum therapeutic utility of these drugs. Before studying the various approaches to enhance dissolution it is necessary to understand the basic process of dissolution. Dissolution is a process by which a

solid substance goes into solution. The extents to which the dissolution proceeds, under a given set of conditions are referred to as the solubility of the substance in the solvent i.e. rate of solution (dissolution) and amount that can be dissolved (solubility) are not same. The dissolution rate of a drug is directly proportional to its solubility as per Noyes- Whitney equation and therefore solubility of a drug substance is a major factor that determines its dissolution rate and hence its absorption and bioavailability eventually [6].

The various properties of drug that affect drug dissolution and its rate includes solubility, particle size, polymorphism, salt form, complexation, wettability, etc [7].

For complete absorption and good bioavailability of orally administered drug, the drug must be dissolved in gastric fluids. Dissolution of drug is the rate-controlling step which determines the rate and degree of absorption. Drugs with slow dissolution rates generally show erratic and incomplete absorption leading to low bioavailability when administered orally. Since aqueous solubility and slow dissolution rate of BCS class II and class IV drugs is a major challenge in the drug development and delivery processes, improving aqueous solubility and slow dissolution of BCS Class II and Class IV drugs have been investigated extensively. Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble drugs which include solid dispersion, micronization, lipid based formulations, melt granulation, direct compaction, solvent evaporation, coprecipitation, adsorption, ordered mixing, solvent deposition inclusion complexation and steam aided granulation. In these techniques carrier plays an important role in improving solubility and dissolution rate [8].

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to promptly achieve and then maintain the desired drug concentration [9, 10]. The route of administration has a significant impact on the therapeutic outcome of a drug [11]. Most of these drug delivery systems are composed of polymer, which contain the drug in the form of a dispersion of the solid drug particles either in a solid or in liquid medium [12].

Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. In solid dispersion method, the drug is dispersed in extremely fine state in an inert water-soluble carrier in solid state. In order to achieve increased dissolution rate, sustained release of drugs and thus improve solubility and stability [13]. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs [14]. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols and related compounds and polymers like mannitol, urea, polyvinyl pyrrolidone (PVP), polyethylene glycols (PEG), and ß-Cyclodextrin used as carriers for solid dispersions. By this approach the dissolution rate and bioavailability of poorly soluble drug can be increased.

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.

Methods of Preparing Solid Dispersions: [15]

Physical Mixture: This method involves mixing, an accurately weighted quantity of drug and carrier in suitable/ required proportion in a glass mortar and sieved through mesh No. 100.

Physical mixture method was used by K.Himasanker who studied solid dispersion of Glipizide with PVP (K-90) and PEG 6000 as carriers.

Fusion Method [16]:

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. A sulphathiazole-urea mixture of eutectic composition at above its eutectic temperature, solidified the dispersion on an ice bath and pulverized it, to a powder, since a super saturation

of the drug can be obtained by quenching the melt rapidly (when the solute molecules are arrested in a solvent matrix by instantaneous solidification), rapid congealing is favoured. Fusion method was used by Shoba Rani who melted clofazimine with mannitol and PEG 6000[17].

Solvent evaporation method:
A Solid dispersion prepared by solvent removal process was termed as "co-precipitates". They should more correctly be designated as "co-evaporates", a term that has been recently adopted. The solvent process uses organic solvents, the agent to intimately mix the drug and carrier molecules. The choice of solvent and its removal rate are critical to quality of dispersion.

A solvent process was used by Kuchekar BS who dissolved paracetamol and β-cyclodextrin in 25% ammonia[18].

Melting-solvent Method [19]:
About 5-10% (w/w) of liquid compounds could be incorporated into PEG 6000 without significant loss of its solid property. Hence, it is possible to prepare solid dispersion by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of PEG, obtainable below 70ºC, without removing the liquid solvent. Melting solvent method was used by K. Venkatesh Kumar who formulated and evaluated Nalidixic acid-PEG 6000 surfactant system [20].

Kneading Method [21]:
Here the required quantity of polymer was weighted as per ratio required and water was added to get dough like consistency. To the mass, weighted quantity of drug was added. The mixture was kneaded in glass mortar for 1 hour and then completely dried in hot air oven at 60º for 2 hours then dried mass was sieved through 120 meshes. Kneading method was used by M.M. Soniwala who studied on various approaches in dissolution enhancement of Rofecoxib by β-cyclodextrin as carrier.

Methods of Determination of Types of Solid Dispersion [15]:
Various methods, which can contribute information regarding the physical nature of the solid dispersions, are thermo analytical methods (Thermal Analysis, DSC, X-ray Diffraction Methods, Spectroscopic Methods and Microscopic Methods).

Objectives:
Fluconazole is a synthetic triazole antifungal drug used in the treatment and prevention of superficial and systemic fungal infection. Fluconazole inhibits the fungal cytochrome p450 enzyme 14α-demethylase. This inhibition prevents the conversion of lanosterol to ergosterol, an essential component of a fungal cytoplasmic membrane, and subsequent accumulation of 14α-demethyl sterols.

The major drawback of this drug is its insolubility in water. Increasing the water insoluble or slightly soluble compounds is a major concern for pharmaceutical researches.

The techniques generally employed to enhance the solubility of poorly water soluble drugs are use of surface active agent, hydrates and solvates, polymorphism, complexation, solid dispersion. Among this solid dispersion is a unique technique used to increase solubility, dissolution and bioavailability of poorly water-soluble drugs. Conventional methods for preparing solid dispersion include physical mixture, fusion method, solvent evaporation method, melting solvent method and kneading method.

Hence, in the present investigation an attempt will be made to develop solid dispersion of fluconazole to overcome solubility problems of drug and to treat fungal infections of skin more effectively

MATERIALS AND METHODS:
Fluconazole was procured as a gift sample from Rajesh chemicals co, Mumbai, India. Polyvinyl pyrrolidone, polyethylene glycol 6000, HPMC was purchased from Loba Chem Pvt. Ltd (Mumbai).Urea, mannitol, were purchased from S.D. Fine chemical Pvt. Ltd, (Mumbai), ß-cyclodextrin, were purchased from Hi-Media Laboratories Pvt. Ltd.

All the chemicals used in the present study were of AR Grade.

Preparation of solid dispersions:
Solid dispersions were prepared by various polymer and different method as shown in **Table 1**.

TABLE 1: FORMULATION INGREDIENTS, PREPARATION METHOD OF FLUCONAZOLE SOLID DISPERSIONS

Batch Code	Composition	Method	Ratio
F1	Fluconazole + Mannitol	Physical mixture	1:1
F2	Fluconazole + Urea	Physical mixture	1:1
F3	Fluconazole + PEG 6000	Physical mixture	1:1
F4	Fluconazole + PVP – K30	Physical mixture	1:1
F5	Fluconazole + ß-cyclodextrin	Physical mixture	1:1
F6	Fluconazole + Mannitol	Solvent evaporation method	1:2
F7	Fluconazole + Urea	Solvent evaporation method	1:2
F8	Fluconazole + PEG 6000	Solvent evaporation method	1:3
F9	Fluconazole + PVP – K30	Solvent evaporation method	1:3
F10	Fluconazole + ß-cyclodextrin	Solvent evaporation method	1:3
F11	Fluconazole + Mannitol	Fusion method	1:3
F12	Fluconazole + Urea	Fusion method	1:5
F13	Fluconazole + PEG 6000	Fusion method	1:5
F14	Fluconazole + PVP – K30	Fusion method	1:5
F15	Fluconazole + ß-cyclodextrin	Kneading method	1:1

Physical mixture [22]:
Physical mixtures were prepared by mixing the appropriate amount of Fluconazole and polymer in pestle and mortar and pass through the sieve # 60.

Fusion method:
Accurately weighed amount of mannitol, urea, PEG-6000, PVP-K30 and ß-cyclodextrin were melted in a porcelain dish at 80 - 85˚ and to this, calculated amount of Fluconazole were added with through mixing for 1-2 min followed by quick cooling.[23] It were kept in a dessicator under vacuum for 24 hrs. Then, solid dispersion formulations were pulverized using a porcelain mortar and pestle. The pulverized powder were sieve using # 60.[24]

Solvent evaporation method:
The drug and the excipients were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40 - 45˚ with continuous stirring to obtain dry granules. [23] The resulting solid dispersion were stored in airtight container till further use.[25]

Kneading method:
ß-cyclodextrin was added to the mortar, and small quantities of 50% v/v ethanol were added while triturating to get slurry like consistency. Then slowly the drug was incorporated into the slurry, and trituration was continued further for 1 hrs. The slurry was then air dried at 25˚C for 24 hrs. Pulverized, and passed through sieve using # 100 and stored in a dessicator over fused calcium chloride.[26]

Evaluation of fluconazole solid dispersions:
Physical Appearance:
All the batches of Fluconazole solid dispersions were evaluated for colour and appearance.

Percent Practical Yield (PY): [27]
Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] ×100

Drug Content: [28]
The Physical mixture and solid dispersion equivalent to 25 mg of model drug were taken and dissolved separately in 25 ml of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were

determined at 261 nm by UV spectrophotometer. The actual drug content was calculated using the following equation as follows:

$$\% \text{ Drug content} = [\text{Mact} / \text{Melt solvents}] \times 100$$

$$= \frac{\text{Actual Fluconazole content in weight quantity of solid dispersion}}{\text{Theoretical amount of Fluconazole solid dispersion}} \times 100$$

In-vitro Dissolution Study: [29]

Dissolution studies were performed assuring sink condition according to the paddle method Dissolution Appratus using Campbell electronics, DR-6. The dissolution medium was 900 ml 5.0 pH citrate phosphate buffer containing 1% Tween 80 kept at 37˚C ± 0.5˚C. The solid dispersions equivalent 100 mg of Fluconazole was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the basket was rotated at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 260 nm using PG Instruments limited, T-80 UV-visible spectrophotometer, the samples withdrawn were replaced by fresh buffer solutions. Each preparation was tested in triplicate and then means values were calculated.

Infrared spectroscopy (IR): [30]

FT-IR spectra of pure Fluconazole, mannitol with its Solid dispersions were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm-1.

Differential scanning calorimetry (DSC): [31]

Thermal analysis of Fluconazole and the solid dispersion were carried out using differential scanning calorimetry method. Samples were examined using a Pyris 6 DSC (model) Perkin Elmer. Samples equivalent to approximately 3-4 mg Fluconazole were placed in aluminum pans and heated from 30 to 250˚C with a heating rate of 10˚C/min.

The onset temperature and peak temperature of the melting endotherm were to be reported.

RESULTS:

TABLE 2: DRUG CONTENT UNIFORMITY STUDIES AND PERCENTAGE PRACTICAL YIELD OF FLUCONAZOLE SOLID DISPERSION

Formulation Code	Drug Content uniformity (%) Mean ± SD	% Practical Yield
F1	94.71	95.86
F2	93.476	94.75
F3	92.363	93.95
F4	95.653	95.10
F5	97.066	96.15
F6	94.170	93.75
F7	93.410	93.10
F8	94.803	91.25
F9	96.530	94.05
F10	93.346	93.05
F11	99.816	96.95
F12	86.240	85.15
F13	92.440	92.10
F14	98.347	95.50
F15	99.297	94.75

TABLE 3: *IN-VITRO* DRUG RELEASE PROFILE OF FLUCONAZOLE SOLID DISPERSION F1 TO F5:

Time (T) (min)	F1 Cumulative % Drug release ± SD	F2 cumulative % Drug release ± SD	F3 cumulative % Drug release ± SD	F4 cumulative % Drug release ± SD	F5 cumulative % Drug release ± SD
0	0.000	0.000	0.000	0.000	0.000
10	15.59 ± 1.73	16.30 ± 2.24	14.66 ± 2.54	16.29 ± 2.79	23.11 ± 1.00
20	23.97 ± 3.37	27.33 ± 5.47	27.33 ± 1.31	28.93 ± 8.86	34.23 ± 1.89
30	34.88 ± 2.93	37.77 ± 1.46	36.17 ± 3.54	39.70 ± 3.17	43.99 ± 7.03

40	42.10 ± 4.51	46.98 ± 6.16	42.11 ± 1.73	47.99 ± 8.41	55.98 ± 0.85
50	45.22 ± 0.55	50.93 ± 7.36	48.17 ± 1.10	52.26 ± 6.01	62.97 ± 2.01
60	50.28 ± 1.62	55.99 ± 3.88	56.99 ± 1.66	55.99 ± 2.56	69.99 ± 4.04

*Average of three replicates

TABLE 4: *IN-VITRO* DRUG RELEASE PROFILE OF FLUCONAZOLE SOLID DISPERSION F6 TO F10:

Time (T) (min)	F6 cumulative % Drug release ± SD	F7 cumulative % Drug release ± SD	F8 cumulative % Drug release ± SD	F9 cumulative % Drug release ± SD	F10 cumulative % Drug release ± SD
0	0.000	0.0000	0.000	0.0000	0.0000
10	49.99 ± 10.02	47.99 ± 3.02	53.48 ± 2.85	54.90 ± 2.03	49.99 ± 3.24
20	60.00 ± 5.07	56.94 ± 2.11	64.24 ± 4.08	61.98 ± 3.77	64.94 ± 1.51
30	69.99 ± 9.37	67.89 ± 1.46	69.57 ± 5.46	73.94 ± 0.70	70.92 ± 5.47
40	84.97 ± 2.59	90.09 ± 2.70	91.86 ± 2.06	87.97 ± 4.80	83.91 ± 4.56
50	93.97 ± 1.74	94.94 ± 1.60	97.35 ± 2.26	89.99 ± 2.07	92.95 ± 1.66
60	--	--	--	---	--

*Average of three replicates

TABLE 5: *IN-VITRO* DRUG RELEASE PROFILE OF FLUCONAZOLE SOLID DISPERSION F11 TO F15:

Time (T) (min)	F11 cumulative % Drug release ± SD	F12 cumulative % Drug release ± SD	F13 cumulative % Drug release ± SD	F14 cumulative % Drug release ± SD	F15 cumulative % Drug release ± SD	Pure Drug cumulative % Drug release ± SD
0	0.000	0.000	0.000	0.000	0.000	0.000
10	56.99 ± 3.27	47.99 ± 9.61	51.98 ± 4.28	53.89 ± 8.27	55.96 ± 2.01	14.98
20	67.96 ± 3.98	59.94 ± 4.40	58.94 ± 3.25	62.98 ± 4.23	65.97 ± 0.81	27.69
30	77.68 ± 7.80	66.95 ± 9.06	67.89 ± 6.09	71.91 ± 3.90	75.98 ± 5.07	38.70
40	97.77 ± 0.15	86.94 ± 1.20	88.96 ± 4.89	86.92 ± 6.65	89.93 ± 6.28	41.11
50	--	93.94 ± 2.53	94.99 ± 2.93	98.97 ± 0.53	97.93 ± 0.70	44.94
60	--	--	--	--	--	46.99

*Average of three replicates

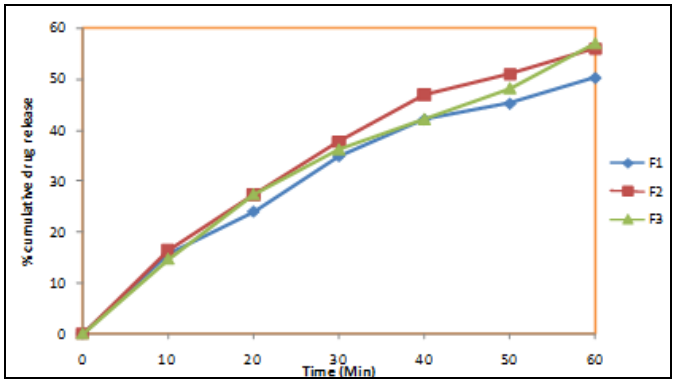


FIG. 1: RELEASE PROFILE OF FLUCONAZOLE FROM (F1, F2, AND F3) SOLID DISPERSION

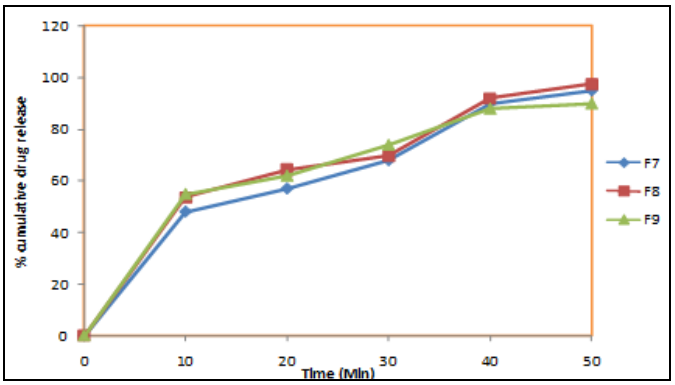


FIG. 3: RELEASE PROFILE OF FLUCONAZOLE FROM (F7, F8, AND F9) SOLID DISPERSION

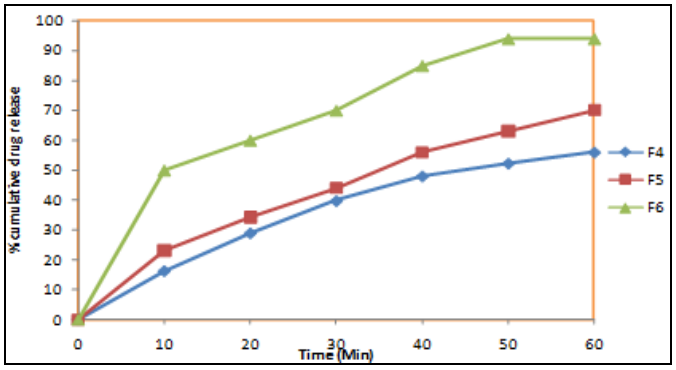


FIG. 2: RELEASE PROFILE OF FLUCONAZOLE FROM (F4, F5, AND F6) SOLID DISPERSION:

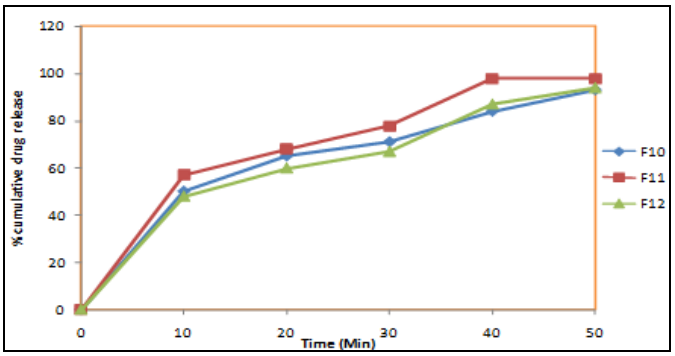


FIG. 4: RELEASE PROFILE OF FLUCONAZOLE FROM (F10, F11, AND F12) SOLID DISPERSION

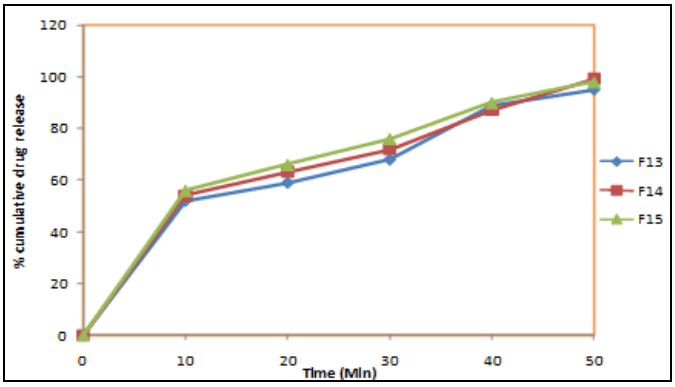


FIG. 5: RELEASE PROFILE OF FLUCONAZOLE FROM (F13, F14, AND F15) SOLID DISPERSION

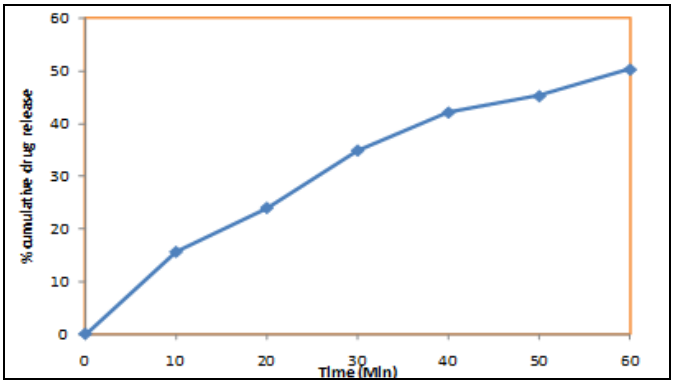
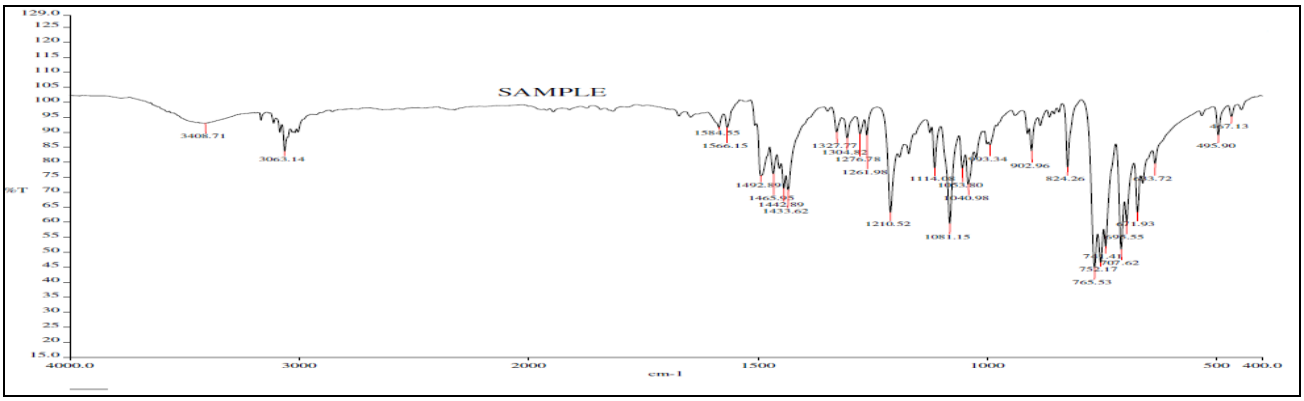
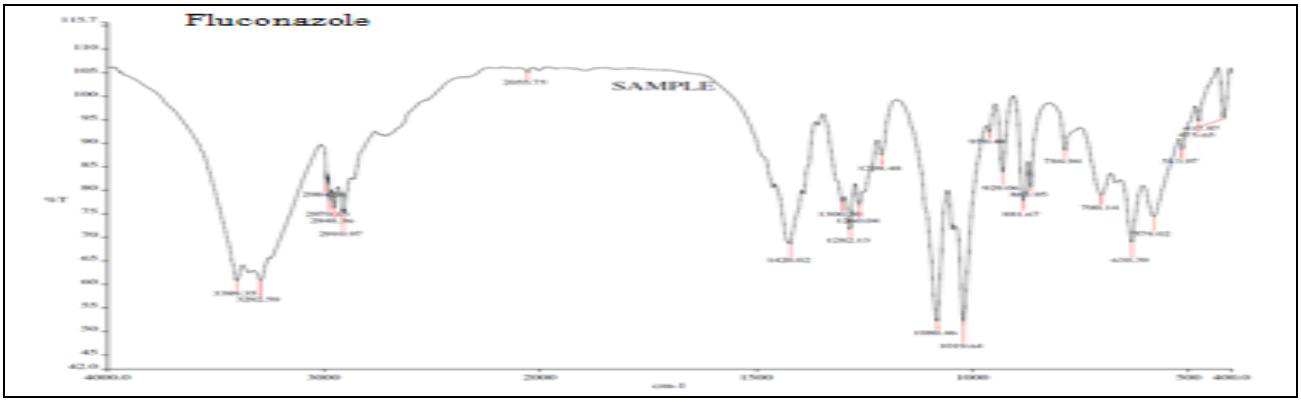


FIG. 6: RELEASE PROFILE OF FLUCONAZOLE PURE DRUG

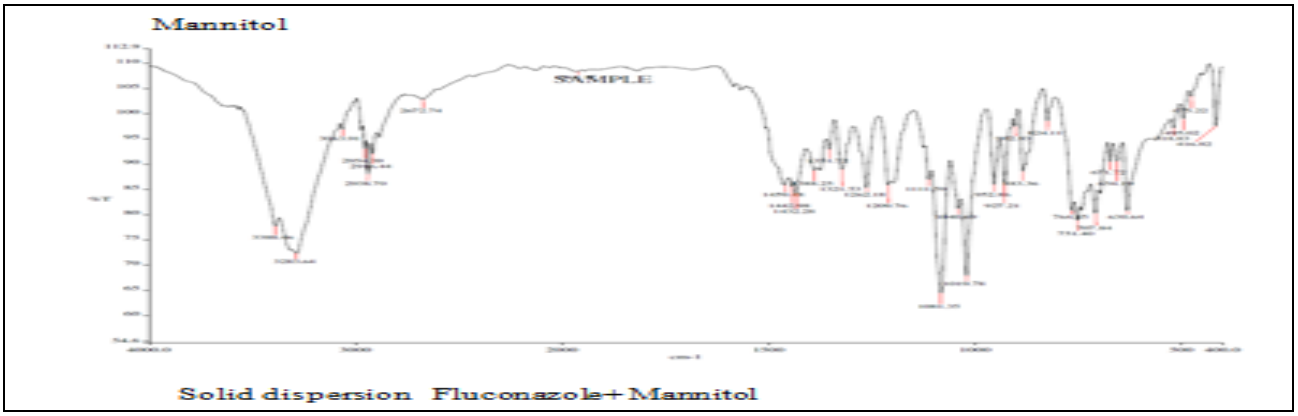
FT-IR Studies:



A



B



C

FIG. 7: IR SPECTRA OF A = FLUCONAZOLE, B = MANNITOL, C = SOLID DISPERSION F11

DSC STUDIES:

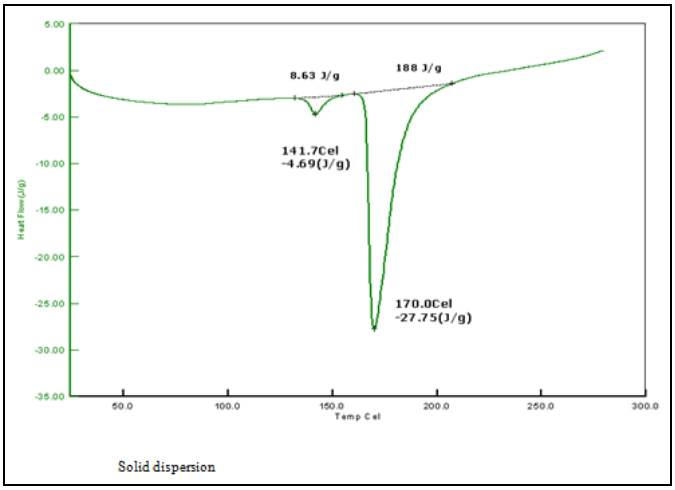


FIG. 8: DIFFERENTIAL SCANNING OF CALORIMETRIC THERMOGRAM OF SOLID DISPERSION(S.D) (F11)

DISCUSSION: In the present investigation, an attempt were made to improve the solubility and dissolution rate of a poorly soluble drug, Fluconazole by solid dispersion method using mannitol, urea, polyethylene glycol (PEG) 6000, polyvinylpyrrolidone K30, β-cyclodextrin as carrier. Solid dispersion of Fluconazole was prepared by Physical mixture, solvent evaporation method, Fusion method and kneading method. The prepared solid dispersion were evaluated for number of parameters like DSC, FT-IR, percent practical yield, drug content uniformity studies, and *In- vitro* drug release studies etc.

Differential Scanning Calorimetry (DSC) Studies:

The drug Fluconazole subjected for DSC study, it started melting of 141.9˚C and completed at 144.5˚C, suggesting that these narrow range of melting is due to the present of single compound in the pure form.

The polymer Mannitol subjected for DSC study, the peak of melting point of mannitol was at 172.4^{o}C.

DSC thermogram of pure drug Fluconazole shows a endothermic peak at 141.9^{o}C and 141.7^{o}C in solid dispersion with mannitol (F11) which indicates that there is negligible change in the peak. From this point we concluded that there is no interaction between drug with mannitol and any other excipients used in the solid dispersion F11.

Infrared (IR) Spectral analysis studies:

FT-IR study was carried out to study the interaction of drug with polymers. The peaks at 3408 cm^{-1} is due to -NH stretching , 3063 cm^{-1} is due to C-H stretching,1584 cm^{-1}is due to C-N cm^{-1} stretching. These are the prominent peaks of the drug fluconazole. All these peaks were also found in the solid dispersion with mannitol (F11).

It clearly indicates that there is no drug interaction with any excipients used in the formulation

Percent Practical yield:

Solid dispersions of Fluconazole were prepared by different method using carriers like Mannitol, Urea, PEG-6000, PVP-K30, and ß-cyclodextrin. In the present work, total 15 formulations were prepared and their complete composition is shown in Table 1. All the Solid dispersions prepared were found to be fine and free flowing powders. The results of percent practical yield studies are shown in Table-2.The percentage Practical yield of the prepared solid dispersions was found to be in the range of 85.15 – 96.95. The maximum yield was found to be 96.95% in F11.

Drug Content Uniformity Studies:

The actual drug content of all the 15 formulations is shown in **Table 2**. The drug content of the prepared Solid dispersion formulations was found to be in the range of 86.24 – 99.81% indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found to be 99.81% in F11.

***In vitro* Dissolution study:**

Drug release from solid dispersions and fusion method was faster than pure drug, **Fig. 1-6** shows the plot of cumulative percent released as a function of time for different formulations. Cumulative percent drug released after 40 minutes were 42.10 – 97.77 for F1 to F15 formulation, while it was 41.11% in 40 minutes for pure drug Fluconazole. Formulation F11 were showed highest dissolution of 97.77 at 40 minutes.

In vitro release study revealed that there was a marked increase in the dissolution rate of Fluconazole from all solid dispersions when

compared to pure Fluconazole itself. From the *in-vitro* drug release profile, it can be seen that formulation F-11 containing mannitol (1:3 ratio of drug: mannitol) show higher dissolution rate compared with other formulations. The increase in dissolution rate was in the order of Mannitol > Urea > ß-cyclodextrin >PEG – 6000 > PVP – K30
Here the preparation and evaluation of Fluconazole solid dispersion were done and the best solid dispersion i.e. F11 (1:3 ratio of Fluconazole: mannitol) by fusion method.

The pure drug and marketed preparation showed a cumulative percent release of 15.87 and 24.90% respectively.

The *in-vitro* drug release data were treated to First order and Higuchi plots. Plots were found to be fairly linear indicating that the drug release follows first order kinetics with diffusion controlled.

CONCLUSION: The data obtain from the study of development and evaluation of Solid dispersions of Fluconazole were prepared by different method using carriers like mannitol, Urea, PEG- 6000, PVP-K30, and ß-cyclodextrin. Carbopol 934, HPMC, MC, NaCMC as gelling agents, the following points can be concluded:

The dissolution rate of Fluconazole from solid dispersion i.e., F1-F15 was significantly higher than that of pure drug.

- Solid dispersion prepared by Fusion method showed faster drug release than the dispersion prepared by Solvent evaporation method then by Kneading method followed by physical mixture.

- The general trend indicated that there was increase in dissolution rate for solid dispersion in the following order of Mannitol > Urea > ß-cyclodextrin >PEG – 6000 > PVP – K30.

- IR studies indicated that no chemical interaction between drug and polymer took place during preparation of solid dispersion of Fluconazole.

- DSC studies indicated that Fluconazole was homogeneously distributed within the carrier in an amorphous state and no drug crystallized out of the dispersion suggesting that drug and polymer exist in the form of a mixture rather than the reaction product.

- The IR study showed that there was no chemical interaction between Fluconazole and polymer.

- Stability studies were performed to assure that the formulation retains its activity, all selected formulations were found to be stable.

Summary: Solid dispersion technology can be used to improve *in vitro* dissolution properties of dissolution dependant poorly water soluble drugs. In the present study, Fluconazole, a poorly water soluble anti-fungal agent was selected. The objective was to investigate the effect of different types of carriers such as mannitol, PEG-6000, Urea, PVP-K30, and ß-cyclodextrin as solubilizer on *in-vitro* dissolution rate of Fluconazole.

Batches of solid dispersion were prepared by physical mixture, fusion, solvent evaporation, and kneading method.

Solid dispersions of Fluconazole were evaluated for physical appearance, percent practical yield, drug content uniformity, *in vitro* dissolution rate, DSC and IR studies.

From the studies carried out on the solid dispersion of Fluconazole using different carrier systems, Fluconazole is homogeneously distributed in an amorphous state within the carrier and no Fluconazole crystallized out of the dispersion. It was concluded that the dissolution rate of Fluconazole from solid dispersions were significantly higher when compared to the amount dissolved from pure Fluconazole.

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How to cite this article:
Sayeed F, Ahmed A and Sayeed A: Formulation and *in vitro* evaluation of solid dispersion of fluconazole. Int J Pharm Sci Res 2016; 7(10): 4170-79.doi: 10.13040/IJPSR.0975-8232.7(10).4170-79.